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Histamine in diabetes: is it time to reconsider?

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23

24 **Abstract**

25 The first studies of histamine and diabetes date back to the 1950s. Since that time the involvement
26 of histamine in diabetes was related to its well known vasoactive properties and permeability
27 leakage effects. In particular, the first evidence for a correlation between histamine and diabetes
28 arose in 1989 when an increase in plasma and leucocyte histamine content was observed. Limited
29 independent evidence followed in the subsequent two decades, focusing on both histamine
30 glyceamic control and macro- and microvascular complications of diabetes. However, recent
31 observations have sparked the question whether it is time to reconsider the functional contribution
32 of histamine in diabetes. We reveal an interesting upsurge in the field which provides scope for new
33 insights into the role of histamine in diabetes.

34

35 **Keywords:** histamine, histamine receptor, diabetes, nephropathy, retinopathy, neuropathy

36

37 **Abbreviations:**

38 ADP= action potential duration; AGEs = advanced glycation end-products; BM = basement
39 membrane; BRB = blood-retinal barrier; CGRP = calcitonin gene related peptide; CKD = chronic
40 kidney disease; DAO = diamine oxidase; DiO = diet-induced obesity; ESRD = end-stage renal
41 disease; H₁₋₄Rs = histamine H₁₋₄Rs; HbA₁ = glycated hemoglobin; HDC = histidine decarboxylase;
42 STZ = streptozotocin; TGF- β = tissue growth factor- β ; TCAs = tricyclic antidepressants; V_{max} =
43 maximum rate of depolarization; VEGF = vascular endothelial growth factor; ZO-1 = zonula
44 occludent-1

46 **1 Introduction**

47 Diabetes mellitus can be considered a family of chronic degenerative disorders associated with a
48 hyperglycemic status caused by either the loss of insulin production due to the destruction of beta
49 pancreatic cells, decreased insulin sensitivity, or both [1, 2]. In 2014, the global prevalence of 8.3%
50 has been estimated and by the end of 2030 this value is expected to rise up to 55% [3], resulting in
51 obvious devastating consequences for healthcare expenditure worldwide. All the antidiabetic drugs
52 currently available, although effective in reducing the risk of acute complications, such as
53 hypoglycemia and hyperglycemia [4], are not effective in reversing the progression of this chronic
54 and degenerative disorder. Indeed, diabetic patients are still at a high risk to develop longstanding
55 complications including cardiovascular disease, such as coronary artery disease, and microvascular
56 diseases, including neuropathy, retinopathy and nephropathy. Therefore, a better understanding of
57 the underlying pathophysiology should contribute to new effective therapeutic approaches. Among
58 the different mediators proposed to contribute to the pathophysiology of diabetes, histamine
59 involvement has always been controversial and considered almost marginal. However, several lines
60 of evidence support the contribution of histamine to the diabetic milieu resulting from the persistent
61 hyperglycemia. For instance, the advanced glycation end-products (AGEs) have been demonstrated
62 to activate mast cells whose degranulation may contribute to a vicious cycle, ultimately resulting in
63 a low-grade inflammation typical of chronic diseases such as diabetes [5]. Therefore, this review
64 aims to revisit the concept of histamine in the pathophysiology of diabetes and, in particular, its
65 complications.

66 **2 Histamine and glycaemia**

67 Histamine is involved in a wide variety of pathophysiological events mostly related to the
68 inflammatory response through four receptors, namely H₁₋₄Rs. The first studies of histamine and
69 diabetes date back to the 1950s. Since that time the involvement of histamine in diabetes was

70 related to its well-known vasoactive properties and permeability leakage effects correlated to
71 microvascular complications. In particular, the first evidence for a correlation between histamine
72 and diabetes came in 1989 through the work of Gill and colleagues when they reported an increase
73 in plasma and leucocyte histamine content which was claimed to contribute to the underlying
74 pathogenesis evoking endothelial permeability [6]. These findings were in keeping with *in vivo*
75 studies of experimental diabetes suggestive of an increased histaminergic tone in diabetic rodents.
76 Indeed, histamine was found to be increased in plasma, kidney, brain, lung, heart, pancreas and
77 intestine [6, 7] of diabetic rats. Independent evidence also suggested a parallel imbalance of the
78 anabolism and catabolism of this amine with an increased synthesis and a simultaneous decreased
79 catabolism [8-11]. For instance, a significant drop in intestinal diamine oxidase (DAO) activity [7]
80 as well as an increase of histidine decarboxylase (HDC) activity in various tissues [12] were
81 observed, thus providing evidence for a nascent histamine pool. The very recent observation of a
82 reduced prevalence of hyperglycemia in HDC^{-/-} NOD mice (an animal model of spontaneous type 1
83 diabetes) in comparison with the wild-type counterpart [13] strongly lends weight to this original
84 hypothesis.

85 More intriguingly, it has been reported that histamine plasma and aortic synthesis [10] in diabetic
86 rats are reduced when insulin is administrated [14], thus strongly supporting the hypothesis for an
87 interconnection between histamine and glycaemic status. This hypothesis is further strengthened by
88 the study of Azevedo and colleagues (1990) reporting an increase of pancreatic islet histamine
89 content in streptozotocin (STZ)-induced diabetes rats [15]. Interestingly, recent data suggest the
90 involvement of the peripheral H₃R in the insulin-histamine loop (Supplementary Figure 1). Indeed,
91 Nakamura and colleagues (2014) provided the first evidence for a potential diabetogenic effect of
92 the pancreatic H₃R, through reporting the presence of functional histamine H₃R in this tissue. In
93 particular, it has been demonstrated that H₃R activation in pancreatic beta cells by imetit (PubChem
94 CID 3692) inhibits the insulin secretion associated with high glucose levels in MIN6 cells [16].
95 Moreover, the same authors reported H₃R expression in pancreatic alpha cells, indicating that H₃R

96 activation may reduce glucagon production by α TC1.6 cells in a non-hyperglycemic condition [17].
97 Notably, although the H₃R has been known to play a critical role in homeostatic regulatory
98 functions, such as control of food intake and maintenance of body weight [18], its contribution to
99 diabetes is controversial [18-24] and still far from being fully understood. Indeed, the H₃R inverse
100 agonist clobenoprit (PubChem CID 2790) has been demonstrated to increase the hypothalamic
101 histamine release and reduce the energy intake in normal and leptin-resistant mice with diet-induced
102 obesity (DiO) [25]. So far, some newly synthesized H₃R antagonists have been specifically tested
103 in diabetic animal models demonstrating an effectiveness in reducing non-fasting glucose levels by
104 potentially blocking the increase of HbA_{1c} [26]. More interestingly, the strategy of an H₃R
105 antagonism combined with a phenylsulfonyleurea (well-known insulinotropic drugs) moiety has
106 been explored [27]; although an effective prototype remains elusive. On the contrary, the activation
107 of H₃Rs in mice has been reported to decrease food intake and increase energy expenditure. Chronic
108 dosing with a H₃R agonist reduces body weight, fat mass, hyperleptinemia, and hyperinsulinemia in
109 DiO mice [28]. Conversely, the protean H₃R agonist proxyfan (PubChem CID 6421522) in mice
110 improves glucose excursion increasing plasma insulin levels without affecting plasma glucagon
111 levels [29]. Furthermore, the mildly obese H₃R-deficient mice also demonstrate leptin and insulin
112 resistance with impaired glucose tolerance [28]. Notably, the majority of these data were obtained
113 before the clear demonstration of H₃R peripheral expression [16, 30-34]. In particular, the
114 pancreatic localization of the H₃R raises the question of contradictory effects mediated by
115 peripheral and central H₃R.

116 Conflicting data concerning the involvement of H₂R on glycaemia has also arisen. Its antagonism
117 was reported to decrease [35], not affect [36, 37] and increase [38, 39] glucose levels. In
118 comparison, the clinical experience with antipsychotic drugs generated clearer evidence for the
119 involvement of the central H₁R in the development of a diabetic phenotype [40]. Consistently, it has
120 been found that the intra-ventricle or –hypothalamic administration of an H₁R agonist induces
121 satiety evoking an anti-obesity effect [41, 42]. Moreover, a strategy based on the contemporary H₁R

agonism and H₃R antagonism was demonstrated to have the potential to reduce obesity also in patients with comorbidities such as diabetes [43].

3 Histamine and diabetes complications

As mentioned above, despite the effectiveness of the different anti-diabetic strategies in controlling glycaemic levels, due to the glucose variability, patients are still exposed to a high risk of developing one or more of the longstanding and serious complications [4]. According to the definitions by the World Health Organization, the complications can be divided into macrovascular complications (including coronary artery disease, peripheral arterial disease and stroke) and microvascular complications (including diabetic nephropathy, neuropathy and retinopathy). Notably, for each new case of one given complication, a higher probability to display another one has been clearly documented [44].

Interestingly, a higher content of histamine in the anatomical districts involved in the diabetic longterm complications has been reported in different studies [6, 7]. Independently from the source of histamine within these districts, due to an activation of mast cells, a recruitment of basophils, an imbalance in the amine anabolism/catabolism or all three, the increased histaminergic tone is a common feature of the different complications and deserves to be further clarified. In particular, based on its vascular actions, histamine has been suggested to be a key triggering stimulus for the functional microangiopathy in diabetes mellitus, from retinopathy to nephropathy. However, its complete functional contribution to diabetes microvascular complications is yet to be elucidated.

3.1 Histamine and macrovascular complications

Cardiovascular diseases (CVD) are one of the leading cause of death in diabetics, with an increased rate of heart disease or stroke from two- to four-fold compared to non-diabetic patients [45]. Notably, histamine has been reported to regulate several cardiovascular and endothelial functions through concerted actions on both smooth muscle and endothelial cells. These actions result in

146 vasoconstriction or vasodilation based on histamine level, diameter and initial vessel tone, and
147 relative location within the coronary circulation [46]. Again the first evidence for histamine
148 involvement in diabetic macrovascular complications comes from the 1980s studies, when the
149 histamine metabolism in both aortic endothelial and subjacent smooth muscle cells of control and
150 diabetic rats was studied [47]. Despite such intriguing initial results, the hypothesis suggested was
151 not further developed, with sparse, indirect and almost contrasting data remaining in the literature.

152 The evidence for a role of histamine stems from mast cell activation during the coronary blood
153 vessel inflammation underling the atherogenesis process [48, 49], but also from its release from
154 activated platelets [50]. Indeed, the number of mast cells was found to be increased in the narrow
155 parts of blood vessels or at the site of plaque rupture in patients suffering from ischemic heart
156 diseases [51, 52]. Notably, histamine release was demonstrated to significantly increase in coronary
157 circulation during myocardial ischemia irrespective of the incidence of risk factors such as
158 hypertension, type 2 diabetes, or dyslipidaemias [53].

159 Among the different receptors, historically the macrovascular effects of histamine seems to be
160 mostly related to the H₁R and H₂R, but no specific studies were designed to investigate the whole
161 histamine receptor family and only one observation claims the ability of H₃R to regulate the
162 coronary vascular response [54]. H₁R has been reported to mediate the overexpression of the
163 adhesion molecules [55] and the activation of nitric oxide synthase [55-57] evoked by histamine in
164 vascular endothelial cells. H₂R has been demonstrated to cause coronary dilation in both an
165 endothelium independent [56] and dependent [54] manner.

166 Apart from atherosclerosis, patients with diabetes mellitus also exhibit QT (QTc) interval
167 prolongation and increased QTc dispersion. Interestingly, HDC^{-/-} mice with aging showed a
168 decrease in maximum rate of depolarization (V_{max}) and action potential duration (ADP)₉₀
169 prolongation comparable to those observed in the wild-type counterpart following diabetes
170 induction by STZ administration [58]. This observation is still far from being conclusive, but it is in

171 keeping with the suggested arrhythmogenic potential of histamine [59, 60]. Although no specific
172 receptor involvement have been described, histamine has been reported to induce Purkinje-fibers
173 depolarization drive to ventricular tachycardia [61]. In mastocytosis patients, when a massive mast
174 cells recruitment and degranulation occur, cardiac arrest has been observed [62]. Moreover, atrial
175 fibrillation was described consequently to anaphylaxis reaction to venom and pollen
176 immunotherapy in patients with established hyperhistaminemia [63]. Finally, a recent study
177 pointing at a connection between histamine and diabetes macrovascular complications concluded
178 that manipulation of cardiac mast cell function with nedocromil (PubChem CID 50294), a mast cell
179 stabilizer, is sufficient to attenuate cardiomyopathy stimulated by diabetes [64].

180 Collectively, in the literature, there are not enough data to support any conclusive dissertation on
181 the role of histamine in the development/maintenance of the macrovascular complication of
182 diabetes, with the majority of its effects ascribable to its general anti-inflammatory properties.

183 **3.2 Histamine and microvascular complications**

184 The vasoactive properties of histamine led to the hypothesis advocating its contribution to the
185 development and maintenance of diabetes-related microvascular complications. As discussed
186 above, the role of the amine was investigated in the different end-organ(s).

187 ***3.2.1 Diabetic neuropathy***

188 Diabetic neuropathy is an heterogeneous family of nerve disorders resulting in improper locomotor
189 and visceral organ dysfunctions at the level of peripheral, central, and visceral sensorimotor and
190 motor nerves [65]. According to this definition we can recognize peripheral, autonomic, proximal,
191 or focal neuropathy. Among these different neuropathies the peripheral subtype is the most
192 common. As a consequence of the peripheral nerve degeneration, triggered by persistent
193 hyperglycaemia, and according to the affected nerves, diabetes patients suffer from pain, weakness,
194 and eventual loss of sensation in addition to severe chronic pain syndromes.

195 The wheal response to intradermal application of histamine in diabetic patients have been assessed
196 since 1930 [66], but its involvement in pain transmission was clearly recognized only by Schwartz
197 and collaborators in 1991. So far many strands of evidence have pointed to histaminergic
198 neurotransmission as an important factor in the control of pain [67-70]. Indeed, diabetic patients
199 have been described to be less responsive to histamine as well as other neurogenic inflammation
200 mediators such as substance P. In addition, a bidirectional relationship between different
201 neurotransmitters and histamine exists [71]. The mRNA of H₁R has been detected in many
202 substance P positive neurons [72] and histamine has been shown to mediate the release of substance
203 P and glutamate [73]. Also, the expression of H₁R and/or H₃R within calcitonin gene related peptide
204 (CGRP) positive neurons [72] was determined. CGRP and histamine can establish a vicious circle
205 inducing one another [70, 74, 75].

206 Although histamine has been reported to modulate nociception through all four types of its receptor,
207 H₁R [69, 76-78], H₂R [76, 78, 79], H₃R [78, 79] and H₄R [80-85], in 2014 the H₃R antagonists were
208 reported as very promising for neuropathic pain [86]. However, only one study was designed to
209 evaluate the antinociceptive effect of the H₃R in a diabetic model. This respective study showed
210 that the selective agonist immpip (PubChem CID 3035842) reversed formalin-induced
211 hyperalgesia in both phases of the formalin test [87]. This effect could be associated with both H₃R
212 peripheral activation, resulting in a reduction in inflammatory peptides release, and H₃R central
213 activation, leading to the inhibition of pain transmission [88-92]. Consistent with this theory,
214 immpip (PubChem CID 3035842) was found to inhibit mechanical, not thermal sensitivity in rats,
215 but was shown to affect neither mechanical nor thermal sensitivity in mice [93]. Moreover, the role
216 of H₃R receptor in nociception is still controversial, with different antagonists, including
217 GSK189254 (PubChem CID 9798547), GSK334429 (PubChem CID 11452311) and ABT-239
218 (PubChem CID 9818903), demonstrated to be effective in reducing the sensitivity to mechanical
219 stimuli [94] or in relief from surgically- and virally-induced neuropathic pain as well as
220 inflammatory pain [82, 95, 96], respectively. The discrepancy emerging from the above described

221 literature can be specifically explained by the observation that the H₃R receptor is expressed both as
222 an autoreceptor and heteroreceptor which inhibits the release of histamine [97] and other
223 neurotransmitters, respectively, including acetylcholine, noradrenaline, dopamine and serotonin
224 [98-102].

225 Notably, histamine has also been shown to play a role in autonomic neuropathy. Indeed, the
226 deranged autonomic function of the airways in diabetic patients with autonomic neuropathy has
227 been demonstrated to elicit an exaggerated response to histamine-induced bronchoconstriction
228 [103]. A direct stimulation of bronchial smooth muscle contraction combined with vagal-mediated
229 reflexes after stimulation of rapidly adapting irritant receptors and C-fibers has been argued to be
230 the mechanism underling the histamine-induce bronchoconstriction, while bronchomotor tone is
231 mainly controlled by the parasympathetic nervous system. Therefore, the exaggerated response to
232 histamine in diabetic patients could be due to the widespread autonomic damage to the respiratory
233 parasympathetic and sympathetic pathways (including non-adrenergic non-cholinergic pathways
234 influencing airway tone) and/or denervation hypersensitivity [104-111]. However, despite the above
235 observations the role of histamine in autonomic neuropathy is still far from clear.

236 ***3.2.2 Diabetic retinopathy***

237 Diabetic retinopathy is still one of the major worldwide cause of blindness. Its development can be
238 divided into non-proliferative, with microaneurysms, hard exudates, haemorrhages, and venous
239 abnormalities and proliferative, with neovascularization, pre-retinal or vitreous haemorrhages, and
240 fibrovascular proliferation [112, 113]. Development of glaucoma, retinal detachment, and vision
241 loss may also happen at this stage [114].

242 A possible role for histamine in this context was postulated when diabetic retinopathy was mainly
243 considered a microvascular complication of endothelial dysfunction with capillary basement
244 membrane (BM) thickening, pericyte and endothelial cell loss, blood-retinal barrier (BRB)
245 breakdown and leakage, acellular capillaries, and neovascularization [115, 116]. Indeed, most of

246 these vascular effects are consistent with the vasoactive properties of histamine. Antihistamines,
247 such as diphenhydramine (PubChem CID 3100), astemizole (PubChem CID 2247) and ranitidine
248 (PubChem CID 3001055), have been shown to reduce the leakage of retinal vessels in diabetic rats
249 and humans [117, 118], but also to attenuate blood-brain barrier permeability and to ameliorate
250 cerebral blood flow disturbances [119].

251 In particular, it was reported that histamine specifically affects the zonula occludent (ZO)-1
252 expression in cultured retinal microvascular endothelial cells [120]. Interestingly, the same authors
253 described a similar inhibitory effect on ZO-1 expression for both high glucose (20mM) and low
254 insulin (10^{-12} M) culturing condition [121]. These data provide a mechanistic interpretation of the
255 ability of histamine to induce a BRB dysfunction in both experimental diabetes and diabetic
256 patients [118, 122, 123], suggesting that the increased histaminergic tone consequent to the diabetic
257 milieu could directly account for the BRB breakdown and leakage vascular, for many years
258 considered pivotal in the pathogenesis of diabetic retinopathy. These effects can be considered at
259 least qualitatively equivalent to those observed for the vascular endothelial growth factor (VEGF)
260 on permeability leakage [124].

261 The possible involvement of histamine in diabetic retinopathy is still plausible, although not deeply
262 investigated, when, according to the neurodegenerative nature of this disease, the other components
263 of the retina, such as neurons and glial cells are taken into account. It is currently acknowledged
264 that cellular, molecular, and functional changes are evidenced in all the retina cellular
265 compartments [115, 116, 125-127] at an early stage of diabetic retinopathy. Intriguingly, an
266 increase in histamine synthesis was observed within the retinas of diabetic rats [117, 128]. This was
267 due to an over-expression of the HDC enzyme in both the retinal neurons and glia [129]. As
268 mentioned above for plasma, aorta and pancreas, an insulin-histamine loop does exist also within
269 the retina. The histamine overproduction induced by diabetes was decreased by both the HDC
270 inhibitor or insulin administration in experimental diabetes [128].

271 Therefore, collectively the data in the literature suggest that histamine could at least participate in
272 the neural cell contribution to the diabetes-induced vascular leakage.

273 **3.2.3 Diabetic nephropathy**

274 Diabetic nephropathy is one of the most important causes of chronic kidney disease (CKD), and
275 therefore of end-stage renal disease (ESRD) in Western nations. It has been estimated that the risk
276 of developing CKD is increased by a factor of 12-fold in type 1 diabetes and 6-fold in type 2
277 diabetes, compared with non-diabetic individuals [130]. About one-third of diabetic patients begin
278 to show persistently high urinary albumin excretion, thence being at high risk to develop *in primis*
279 diabetic ESRD, but also cardiovascular diseases and premature mortality, even without progression
280 to ESRD [131].

281 Intriguingly, the first evidence for a possible role of histamine in the development of diabetic
282 nephropathy arose from studies performed in STZ diabetic rats in which histamine levels, consistent
283 with the generalized increase of the amine induced by diabetes, were found to be significantly
284 increased in the kidney [132, 133]. Again, a greater tissue HDC activity without a concomitant
285 decrease in histaminase activity could account for this event [133] especially at the glomerular level
286 which has been identify as the major site of intrarenal histamine synthesis and accumulation [109,
287 134]. The demonstrated ability of histamine to increase salt and water excretion [135-137], decrease
288 the ultrafiltration coefficient by reducing the total filtration surface area [137], and increase renin
289 release [138] led to the hypothesis of a direct involvement of histamine in regulating the renal
290 microcirculation. For a long period, histamine was claimed to affect the glomerular
291 microcirculation. However, recent evidence suggest and support the hypothesis of direct effects of
292 histamine on glomerular integrity and function, far beyond simply modifying the glomerular
293 hemodynamic microcirculation [139].

294 At the tubular level, the first evidence of a histamine detrimental effect on tubular integrity and
295 function was already available in the 1960s and 1970s when several reports suggested that mast

cells may be involved in kidney diseases, but as mast cells were not easily detected by routine histochemical staining, they were ignored or forgotten by nephrologists for many years [140]. In the normal kidney, mast cells are constitutively present at a low number. However, their density increases in the renal cortical tubulointerstitium, in the periglomerular and perivascular area, but not in glomeruli, in a variety of human renal diseases including diabetic nephropathy [140-142]. Moreover, mast cells have occasionally been found in the wall of atrophied tubules [142]. In particular, it has been shown that with disease progression, the number and degranulation status of mast cells increased, suggesting that histamine released by mast cells into the tubular interstitium may promote renal inflammation and fibrosis [141, 142]. Indeed, histamine has been reported to promote fibrosis affecting the tissue growth factor (TGF)- β /Smad3/4 axis in the lung [143].

In the past several decades, all the renal effects of histamine were ascribed only to H_1R and H_2R , both identified in the glomeruli [12, 132]. Consistent with results obtained in rats [138], it was found in humans that the H_2R is the subtype present in glomeruli and involved in the cAMP accumulation subsequent to the increasing histamine [144]. Moreover, it has been demonstrated that histamine modulates mesangial cells and glomeruli via H_1R [145]. In the last few years, convergent lines of evidence strongly support the conclusion that all four histamine receptors are present and functional in the human nephron, although with a differential anatomical topology [34]. Notably, among them, both the H_3R and the H_4R have been reported to be profoundly upregulated at the tubular level in STZ treated rats, which also displayed parallel renal damage (mostly again at the tubular level) [33, 146]. These latter data led to a new interest in histamine in kidney (patho)physiology supporting the hypothesis that it could directly and specifically contribute to the onset/progression of diabetic nephropathy.

4 Conclusion

Is it really the time to reconsider the functional contribution of histamine in diabetes? Indeed, although still far from conclusive, different elements point to a clear role of histamine in diabetes

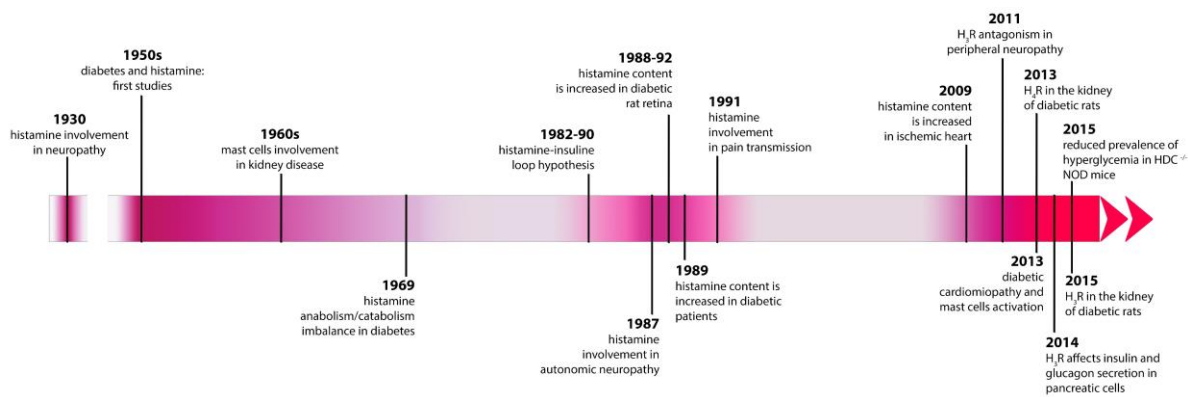
321 and diabetic complications etiopathogenesis. The evidence is strong in some cases, sometimes
322 independent, but sometimes contradictory; despite this heterogeneity, when viewing the timeline of
323 interest for histamine involvement in this disease (Figure 1) it appears phasic with a clear upturn
324 and renewal in interest in the last couple of years, thanks to the very recent discovery of a direct
325 effect of histamine on glycaemia [13, 16, 17] as well as a profound up-regulation of both H₃R and
326 H₄R in the diabetic animal kidney [33, 146]. As a whole, the revisit of the literature herein clearly
327 shows growing independent lines of evidence for a bidirectional connection between histamine and
328 diabetes (Table I).

Table I. The diabetes-histamine loop: the state of the art						
Diabetes complication	Diabetes affects histamine	Histamine influences the progression	Receptor involved			
			H₁R	H₂R	H₃R	H₄R
<i>macrovascular</i>	↑ HDC and histamine in aortic endothelial and smooth muscle cells	atherogenesis coronary dilation, arrhythmogenic activity (QT-prolongation)	++	++	+	n.d.
<i>microvascular</i>						
<u>neuropathy</u>						
<i>peripheral neuropathy</i>		pain control, neurogenic inflammation	n.d.	n.d.	+	n.d.
<i>autonomic neuropathy</i>		↑ bronchoconstriction	n.d.	n.d.	n.d.	n.d.
<u>retinopathy</u>	↑ HDC and histamine	↑ vascular leakage	++			
<u>nephropathy</u>	↑ HDC, histamine, H ₃ R and H ₄ R expression	↑ salt and water excretion, ↓ ultrafiltration coefficient, ↑ renin release	+	+	?	?
++ = strongest evidence; + = spare evidence; ? = under investigation/characterization; n.d. = no data						

329

330

331 Therefore, a pathophysiological role for this amine cannot be discounted anymore and new studies
332 specifically aimed to assess its function in the onset and progression of the longstanding diabetes
333 complications are strictly warranted. The state of the art on histamine in diabetes is recapitulated in
334 Figure 1.



335

336 **Figure 1. Milestones in the story of histamine and diabetes.** Timeline of major events in the
337 history of histamine and its link to diabetes and its complications - 1930s to present day. The phasic
338 interest with the recent upsurge in the last couple of years is depicted.

339

340 As reported in Table I, not all the diabetic complications have been provided with the same level of
341 compelling evidence. Many blind spots remain regarding the role of histamine in macrovascular
342 complications where the effect of the amine seems to be mostly related to its general vasoactive
343 properties rather than to a specific function in diabetes. The discrepancies often observed in the
344 literature can be mostly ascribed to the different models adopted as well as to the doses, the
345 administration route and the actual selectivity of the compound used, which could differentially
346 affect the central and peripheral histaminergic system. More notably, the majority of the evidence
347 for histamine involvement in the different diabetes complications arises from studies not directly
348 aimed to assess its role in diabetic disease. This is in particular the case for diabetic peripheral
349 neuropathy where the studies were designed to assess a general role in nociception and/or

350 neuropathic pain. Other fields, such as retinopathy, have found using new strategies, effective and
351 specific pharmacological tools that have downgraded the antihistaminergic approach to a supporting
352 role. However, since many of the investigations were prior to the discovery of the newest histamine
353 receptor members H₃R and H₄R, [147] there is scope for new insights in histamine and diabetes,
354 and the opportunity to develop new antihistamine drugs to overcome the paucity of effective
355 therapies.

356

357 **Conflict of interest** none

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362 authors contributed and have approved the submitted version of the paper.

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